The points made in the February 17, 2009 Amendment, the December 30, 2009 Request for Reconsideration and the previous declarations are incorporated herein. The record demonstrates that QTc prolongation is a serious side effect which normally will require abandonment of an otherwise promising drug candidate. Moreover, the testing required by the FDA is evidence that a compound's tendency to prolong QTc cannot be predicted, but instead must be empirically determined. The record also demonstrates that those of ordinary skill in the art believe the mechanism of QTc prolongation is based on electrochemical modification of the action potential, and not on a particular administration route of the drug.

Huupponen and Karjalainen fail to disclose or suggest whether fipamezole will prolong QTc. However, one of ordinary skill, aware that oral administration of fipamezole causes dose-dependent QTc prolongation, would reasonably expect oromucosal administration to prolong QTc as well because the particular administration route is not believed to cause QTc. Moreover, he would believe oromucosal administration of fipamezole would cause an equivalent or longer QTc prolongation than oral administration in view of Huupponen's teaching regarding the increased bioavailability of atipamezole (a

fipamezole analog) when oromucosally administered. The unexpected and surprising absence of QTc prolongation when fipamezole is oromucosally administered - in stark contrast to its tendency to prolong Qtc when orally administered - overcomes any *prima facie* case of obviousness raised by the cited references.

The Patent Office *Must* Consider Fipamezole's QTc Prolongation Properties

The Patent Office objection that the claims do not recite a QTc limitation (Official Action, page 6, penultimate sentence) is without merit. See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)("From the standpoint of patent law, a compound and all its properties are inseparable; they are one and the same thing"). Application Example 8 demonstrates fipamezole can prolong QTc when orally administered, but surprisingly does not prolong QTc when oromucosally administered at the same dosage amounts. Independent claim 23 requires oromucosal administration of fipamezole. Accordingly, the Patent Office must consider fipamezole's property of not prolonging QTc when it is oromucosally administered, Papesch, supra.

QTc Prolongation Is Independent from Heart Rate

The Patent Office argument that "QTc is associated with heart rate" (Official Action, page 5, line 4) is scientifically and medically wrong. Appendix II of Dr. Seiler's declaration provides a detailed explanation of the QT interval, and the cardiac safety concerns raised by QT prolongation. Paragraph 12 of his declaration points out QT prolongation (measured in milliseconds) can be induced without a change in heart rate (measured in beats/minute).

Dr. Savola's attached Rule 132 declaration ("Dr. Savola's second declaration") confirms QTc prolongation is independent from heart rate, and can occur *even though heart rate remains unchanged*. He concludes "Nothing concerning QTc prolongation or the absence thereof can be determined or predicted from the heart rate value (or from a change in heart rate) upon administration of a drug." See paragraph Nos. 5-9 of Dr. Savola's second declaration.

The Absence of QTc Prolongation is Unexpected and Surprising

The Patent Office maintains this obviousness rejection based on Huupponen's disclosure that heart rate was unchanged after oromucosal administration of atipamezole, coupled with its incorrect belief that QTc is associated with heart rate. However,

nothing concerning QTc prolongation or the absence thereof can be determined or predicted from heart rate.

Huupponen and Karjalainen both fail to disclose anything regarding QTc prolongation. In fact, Huupponen is limited to teaching oromucosal administration of atipamezole (a fipamezole analog) produces higher plasma concentrations than oral administration of atipamezole. Accordingly, all one of ordinary skill can reasonably predict from Huupponen is that oromucosal administration of fipamezole would also produce higher plasma levels than oral administration of fipamezole.

Oral administration of fipamezole causes dose-dependent QTc prolongation - the higher the plasma concentration, the longer the QT interval is prolonged. Thus, in the dog, oral administration of fipamezole at 5 mg/kg/day dosage prolonged the QTc interval by 14.0 ms, while a 10 mg/kg/day dosage prolonged the QTc interval by 25.0 ms. See paragraph 4F, last subparagraph on page 7, and Fig. 1, of Dr. Savola's declaration filed February 17, 2009.

Given this data, one of ordinary skill in the art would reasonably expect oromucosal administration of fipamezole to prolong QTc by as much or longer than oral administration in view of Huupponen. The absence of any QTc prolongation when fipamezole

is oromucosally administered cannot be predicted from Huupponen. See paragraph Nos. 10-12 of Dr. Savola's declaration.

Dr. Seiler's testimony provides still more evidence that one of ordinary skill would consider fipamezole's lack of QTc prolongation when oromucosally administered surprising and unexpected. This independent expert, with many years of education and relevant experience, is unaware of any other compound in which a change in the mode of administration eliminated a QTc prolongation problem. See paragraph No. 13 of Dr. Seiler's declaration.

In short, the result achieved by the claimed method of oromucosal administration of fipamezole (lack of QTc prolongation) is unexpected and surprising in view of fipamezole's dose-dependent tendency to prolong QTc when orally administered.

The Claims Properly Omit a Dosage Amount

The Patent Office objection that the claims do not recite a dosage amount is also without merit. The inventors discovered oromucosal administration of fipamezole avoids a very serious side effect[1] caused by oral administration of the same compound. Their

[1]Pharmaceutical industry practice is to abandon a drug which prolongs the QTc interval due to the risk of fatal arrhythmia. See

discovery is directed to a novel administration route for fipamezole rather than any criticality of a specific dosage amount or range. Accordingly, method claims 23 and 25-33 properly do not contain a dosage or concentration range.

The dog toxicity studies summarized in Example 8 and discussed in detail in Dr. Savola's and Dr. Seiler's previous declarations fully support the claimed method. More specifically, an independent laboratory followed international guidelines on how to properly assess a drug's tendency to prolong the QT interval. These guidelines include the recording of electrocardiograms from dogs which have been administered the drug under investigation at various doses, including multiples of the anticipated human exposure to the drug. The data show oral administration causes QTc prolongation, with the prolongation increasing with increasing fipamezole plasma concentration once the systemic concentration in blood achieves a certain threshold. The data also show oromucosal administration does not prolong QTc at plasma concentrations equal to and greater than those which caused Qtc prolongation upon oral administration.

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paragraph Nos. 13 and 14 of Dr. Savola's second declaration.

A broad claim range can be supported by a narrower range of data where one of ordinary skill in the art has reasonable basis to extrapolate the data to the entire range, In re Kollman, 595 F.2d 48, 201 USPQ 193 (CCPA 1979). In this case, one of ordinary skill would reasonably extrapolate the QTc data generated in the dog toxicity studies to the clinical situation, in which smaller dosage amounts would be employed. More specifically, one of ordinary skill would believe oromucosal administration of fipamezole would not prolong the QTc interval at *any* clinical dose in view of (1) the absence of QTc prolongation at higher-than-clinical dosages when oromucosally administered to the dog, and (2) the dose-dependent nature of QTc prolongation caused by oral administration of fipamezole. See paragraph Nos. 15-18 of Dr. Savola's second declaration.

Reconsideration and withdrawal of the obviousness rejection of claims 23, 25-29 and 31-33 over Huupponen et al. in view of Karjalainen et al. are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 23 and 25-33 over Huupponen and Karjalainen, further in view of U.S. Patent No. 6,413,988 to de Proost, is traversed for the reasons previously discussed. De Proost is not directed to α_2-adrenergic receptor

antagonists, and does not disclose any information concerning oromucosal vs. oral administration of fipamezole. Accordingly, the additional disclosure of this secondary reference does not detract from the unexpected and surprising result achieved by the claimed method of administration. Reconsideration and withdrawal of the obviousness rejection of claims 23 and 25-33 over Huupponen and Karjalainen, further in view of de Proost, are respectfully requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of the obviousness rejections of claims 23 and 25-33, and issuance of a Notice of Allowance directed to those claims, are requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

The Extension of Time fee is being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Request. Nevertheless, the Commissioner is

authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

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Enclosures:
Petition of Extension of Time
Declaration Pursuant to 37 C.F.R. § 1.132